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Pulmonary Valve Replacement After Operative Repair of Tetralogy of Fallot

Meta-Analysis and Meta-Regression of 3,118 Patients From 48 Studies

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Because the real benefit of pulmonary valve replacement (PVR) in patients with repaired tetralogy of Fallot who develop pulmonary insufficiency remains unclear, it is necessary to analyze the evidence published around the world. We performed a systematic review of studies that reported data about the effect of PVR in patients with repaired tetralogy of Fallot that developed pulmonary insufficiency, until December 2012. The variables chosen to represent the benefit were both right ventricular (RV) and left ventricular measures, QRS duration, and functional class. The principal summary measures were difference in means with 95% confidence interval and p values (considered statistically significant when $p < 0.05$). The differences in means were combined across studies with the weighted DerSimonian-Laird random effects model. Meta-analysis, sensitivity analysis, and meta-regression were completed with the software Comprehensive Meta-Analysis (version 2, Biostat, Inc., Englewood, New Jersey). Forty-eight studies involving 3,118 patients met the eligibility criteria. The pooled 30-day mortality was 0.87% (47 studies; 27 of 3,100 patients); the pooled 5-year mortality was 2.2% (24 studies; 49 of 2,231 patients); the pooled 5-year re-PVR was 4.9% (15 studies; 88 of 1,798 patients). The results of this meta-analysis demonstrate that after PVR: 1) the RV experiences improvement of its volumes and function; 2) the left ventricle experiences improvement of its function; 3) QRS duration decreases; 4) symptoms improve; 5) pre-operative RV geometry modulates the effect of PVR; and 6) there is important heterogeneity of the effects among the studies, and few publication biases. In conclusion, PVR seems to be a positive approach in the analyzed scenario. (J Am Coll Cardiol 2013;62:2227–43) © 2013 by the American College of Cardiology Foundation

Rationale

The current indications of pulmonary valve replacement (PVR) for pulmonary insufficiency in patients with repaired tetralogy of Fallot (TOF) according to the most recent guidelines (1,2) are based overall on the presence of symptoms (Class I). In asymptomatic patients, the indications are restricted to the following situations: decrease in exercise tolerance according to objective tests; right ventricular (RV) function and size deterioration; presence of sustained atrial and/or ventricular arrhythmias; tricuspid regurgitation (at least moderate); and RV outflow tract obstruction (Class IIa).

Despite recommendation classes, the levels of evidence still remain low (level B and C). Therefore, it is necessary to review the current state of published medical data with regard to this subject.

Objectives

This analysis was planned in accordance with current guidelines for performing comprehensive systematic reviews and meta-analysis with regression, including the PRISMA (Preferred Reporting Items for Systematic reviews Meta-Analyses) (3) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) (4) guidelines for randomized and nonrandomized studies, respectively. We aimed to determine the outcomes after PVR and its effect

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Abbreviations and Acronyms

LV = left ventricle/ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

MRI = magnetic resonance imaging

NYHA = New York Heart Association

PRF = pulmonary regurgitation fraction

PVR = pulmonary valve replacement

RV = right ventricle/ventricular

RVEDV = right ventricular end-diastolic volume

RVEF = right ventricular ejection fraction

RVESV = right ventricular end-systolic volume

TOF = tetralogy of Fallot

on indexed ventricular volumes, ventricular function, functional class, and QRS duration in pediatric and adult patient populations after operative repair of TOF.

Methods

Eligibility criteria. With the PICOS (Participants, Interventions, Comparisons and Outcomes) strategy, studies were considered if: 1) the population comprised patients with total repaired TOF that developed at least moderate pulmonary valve insufficiency; 2) patients were submitted to PVR; 3) patients were assessed before and after PVR; 4) outcomes studied included any of the following: 30-day and 5-year mortality rates, 5-year redo-PVR rate, indexed right ventricular end-diastolic volume (RVEDV), indexed right ventricular end-systolic volume (RVESV), right ventricular ejection fraction (RVEF), corrected RVEF, pulmonary regurgitation fraction (PRF), indexed left ventricular end-diastolic volume (LVEDV), indexed left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF), QRS, RV/LV ratio, New York Heart Association (NYHA) functional class; and 5) studies were prospective or retrospective or nonrandomized or randomized controlled trials.

Information sources. The following databases were used (until December 2012): MEDLINE; EMBASE; CENTRAL/CCTR (Cochrane Controlled Trials Register); ClinicalTrials.gov; SciELO (Scientific Electronic Library Online); LILACS (Literatura Latino Americana em Ciências da Saúde); Google Scholar; and reference lists of relevant articles.

Search. We conducted the search with MeSH (Medical Subject Headings) terms ("Tetralogy of Fallot" OR "Tetrallogy, Fallot's" OR "Tetralogy, Fallot" OR "Tetralogy, Fallots" OR "Fallot's Tetralogy" OR "Fallot Tetralogy" OR "Fallots Tetralogy") AND ("Pulmonary Valve Insufficiency" OR "Valve Insufficiency, Pulmonary" OR "Regurgitation, Pulmonary" OR "Pulmonary Regurgitation" OR "Valve Regurgitation, Pulmonary" OR "Valve incompetence, Pulmonary" OR "Pulmonary Valve Incompetence" OR "Pulmonary Valve Regurgitation" OR "Regurgitation, Pulmonary Valve" OR "Insufficiency, Pulmonary Valve" OR "Incompetence, Pulmonary Valve") AND ("Replacement" OR "Replantation" OR "Replantations" OR "Surgical Replantation" OR "Replantation, Surgical" OR "Replantations, Surgical" OR "Surgical Replantations" OR "Reimplantation" OR "Reimplantations").

Study selection. The following steps were taken: 1) identification of titles of records through databases searching; 2) removal of duplicates; 3) screening and selection of abstracts; 4) assessment for eligibility through full-text articles; and 5) final inclusion in study.

One reviewer followed steps 1 to 3. Two independent reviewers followed step 4 and selected studies. Inclusion or exclusion of studies was decided unanimously. When there was disagreement, a third reviewer made the final decision.

Data items. The crude endpoints were 30-day mortality (%), 5-year mortality (%), and 5-year redo-PVR (%). The following mean values of comparative data were also collected with regard to pre-operative and post-operative periods: indexed RVEDV (ml/m^2); indexed RVESV (ml/m^2); RVEF (%); corrected RVEF (%); PRF (%); indexed LVEDV (ml/m^2); indexed LVESV (ml/m^2); LVEF (%); RV/LV ratio; QRS duration (ms); and NYHA functional class (mean).

Data collection process. Two independent reviewers extracted the data. When there was disagreement about data, a third reviewer (P.E.F.C.) checked the data and made the final decision. From each study, we extracted patient characteristics, study design, and outcomes.

Risk of bias in individual studies. Included studies were assessed for the following characteristics: design (prospective or retrospective); presence of randomization (yes or no); multicenter enrollment (yes or no); characteristics of participants (selection bias); characteristics of personnel (performance bias); outcome assessment (detection bias); and incomplete outcome data addressed (attrition bias).

Two independent reviewers assessed risk of bias. Agreement between the 2 reviewers was assessed with kappa statistics for full-text screening and rating of relevance and risk of bias. When there was disagreement about risk of bias, a third reviewer (P.E.F.C.) checked the data and made the final decision.

Summary measures. The principal summary measures were difference in means with 95% confidence intervals and p values (considered statistically significant when $p < 0.05$). The meta-analysis was completed with the software Comprehensive Meta-Analysis (version 2, Biostat, Inc., Englewood, New Jersey).

Synthesis of results. Forest plots were generated for graphical presentations of clinical outcomes, and we performed the I^2 test and chi-square test for assessment of heterogeneity across the studies (5). Each study was summarized by differences in means before and after PVR. The differences in means were combined across studies with weighted DerSimonian-Laird random-effects model (6).

Risk of bias across studies. To assess publication bias, a funnel plot was generated, statistically assessed by Begg and Mazumdar's test (7) and Egger's test (8).

Sensitivity analysis. To evaluate the real RV performance, it has been suggested that the corrected RVEF measure

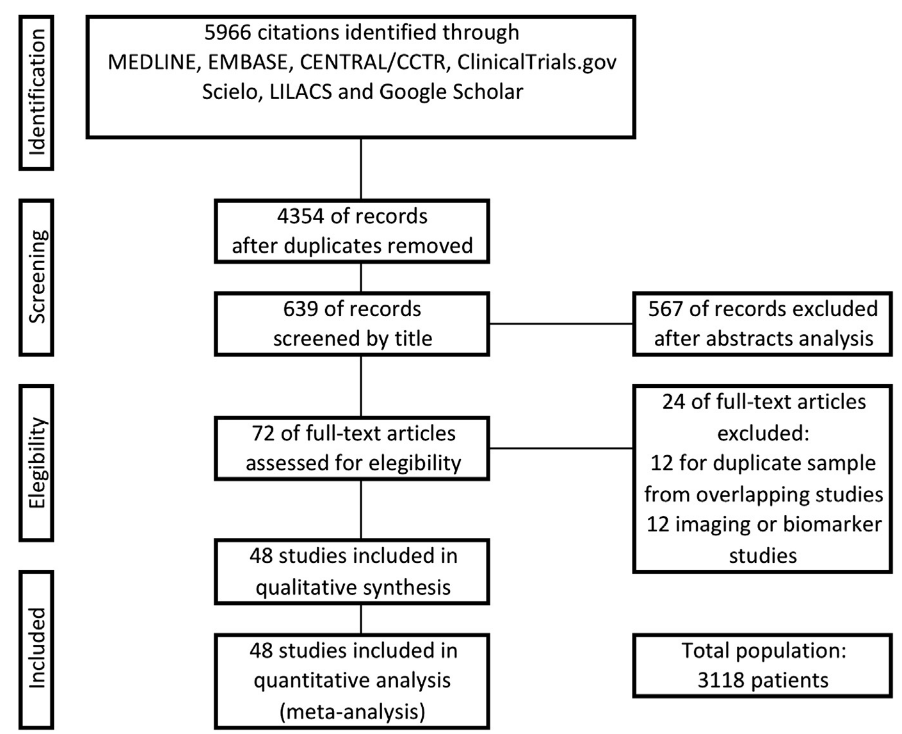

Figure 1 **Flow Diagram of Studies Included in Data Search**

CCTR = Cochrane Controlled Trials Register; LILACS = Literatura Latino Americana em Ciências da Saúde; SciELO = Scientific Electronic Library Online.

should be used in the pre-operative situation (9) because pulmonary and tricuspid regurgitation—beyond shunting over a residual ventricular septal defect—might lead to a compensatory increase in RV cardiac output to maintain net pulmonary forward flow. Without correction for regurgitation and shunting, non-corrected RVEF measure would overestimate pre-operative RV performance, underestimating a possible improvement on RV function after PVR.

Taking into consideration this scenario, we decided to perform an extra analysis to evaluate the changes in RVEF before and after surgery, considering the pre-PVR corrected and non-corrected RV function measure.

Meta-regression analysis. Meta-regression analyses were performed to determine whether the effects of PVR were modulated by pre-specified factors. Meta-regression graphs describe the effect of PVR on the outcome (plotted on the y-axis) as a function of a given factor (plotted as a mean or proportion of that factor on the x-axis).

The pre-determined modulating factors to be examined were: age at TOF repair, time of interval from repair to PVR, age at PVR, sex, additional procedures, pre-operative indexed RVEDV, pre-operative indexed RVESV, and PRF changes.

Results

Study selection. A total of 5,966 citations were identified, of which 72 studies were potentially relevant and retrieved as full-text. Forty-eight (9–56) publications fulfilled our eligibility criteria. Interobserver reliability of study relevance was excellent (Kappa = 0.80). Agreement for decisions related to study validity was very good (Kappa = 0.81). The search strategy can be seen in Figure 1.

Study characteristics. Characteristics of each study are shown in Table 1. A total of 3,118 patients were included from studies, dating from 1997 to 2012, involving patients enrolled from 1960 to 2011. Ten studies were prospective (20.8%), 1 was randomized (2%), and 8 were multicenter (16.7%). Most studies consisted of patients whose mean or median age at PVR was approximately the first and third decade of life and who were mostly male. Eight (16.7%) studies consisted of an exclusively pediatric population, 14 (29.2%) were of an exclusively adult population, and 26 (54.1%) were of a mixed population. In general, we have observed that PVR has been indicated in the following situations: presence of symptoms and/or exercise intolerance during tests and/or those who had RV impairment, taking into account imaging data, with more attention given to cardiac magnetic resonance imaging (MRI) for detecting RV dilation. The overall internal validity was considered moderate risk of bias (Table 2).

Synthesis of results. The pooled 30-day mortality was 0.87% (47 studies; 27 of 3,100 patients); the pooled 5-year mortality was 2.2% (24 studies; 49 of 2,231 patients); the

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Table 1 Studies Characteristics

First Author (Ref. #)	Sample (N)	Sex, Male	30-Day Mortality	5-Yr Mortality	5-Yr Redo-PVR	Additional Procedures	Age at Fallot Repair Mean/Median (SD or Range)		Time Interval TOF Repair to PVR Mean/Median (SD or Range)		Age at PVR Mean/Median (SD or Range)	
Chalard et al. (10)	21	47.6	0	ND	ND	28.6	5.76	ND	ND	ND	30.1	14.1
Lee et al. (11)	170	60.6	1.2	1.2	2.9	55.3	2	0.2–44.1	13.8	4.0–27.5	16.7	4.6–60.2
Quail et al. (12)	51	54.9	0	ND	ND	17.6	2	0.8–4.7	ND	1.5–2.1	19.6	14.1–24.6
Jang et al. (13)	131	67.9	0	0	3.5	79.4	ND	ND	12.5	5.2	14.8	6.7
Tobler et al. (14)	39	59.0	0	ND	ND	ND	5	1–35	27	14–46	33	20-65
Shiokawa et al. (15)	19	ND	0	0	0	31	5.6	5.4	20.8	10.2	26.1	13.6
Jain et al. (16)	153	47.1	4.6	3.3	ND	20	ND	ND	ND	ND	33	18–74
Batlivala et al. (17)	254	64.2	1.2	1.9	3	83.5	ND	ND	ND	ND	15.6	3.3
Frigiola et al. (18)	73	35.6	0	ND	ND	ND	3.9	5.2	ND	ND	23.6	11.5
Chen PC et al. (19)	227	62.6	0	3	6	74	0.8	0.01–37.0	17.5	0.37–46.13	19.4	0.4–58.1
Chen X-J et al. (20)	161	65.8	1.2	1.2	6	ND	ND	ND	ND	ND	ND	ND
Zubairi et al. (21)	169	55.0	0.6	ND	7	12.4	ND	ND	12	0.6–32.1	14.6	0.6–49
Ovcina et al. (22)	24	70.8	0	0	ND	29.2	ND	ND	ND	ND	23.1	6.6
Kane et al. (23)	38	26.3	0	ND	ND	59	6.6	10.6	ND	ND	33.1	13.2
Geva et al. (24)	64	50.0	0	ND	ND	46	1	0–18	20	11.0–47.9	21	11.0–58.0
Shinkawa et al. (25)	73	60.3	0	0	1.3	59	ND	ND	19.9	11.6	17.3	2.1–64.4
Scherptong et al. (26)	90	58.9	0	2.2	ND	47	5.8	5.5	ND	ND	31.4	10.3
Lindsey et al. (27)	42	64.3	0	0	ND	ND	0.73	ND	ND	ND	8	3
Tsang et al. (28)	16	62.5	0	ND	ND	ND	6	5	19	9	24	13
Harrild et al. (29)	98	ND	0	6.1	ND	7.1	4.9	6.5	19.7	9.4	24.6	13
Dos et al. (30)	116	51.7	2.5	ND	0.86	95	9	6	ND	ND	36	11
Meijboom et al. (31)	17	ND	0	0	ND	ND	4.7	3.4	18.6	5.4	27.6	5.8
Graham et al. (32)	93	ND	0	2.1	ND	ND	7.8	ND	ND	ND	27	ND
Knirsch et al. (33)	16	68.8	0	ND	ND	25	1.8	0.9	9.9	2.6	11.7	3.5
Frigiola et al. (34)	25	48.0	0	ND	ND	95	4.3	6.6	ND	ND	21	13
van Huysduynen et al. (35)	30	63.3	0	3.3	ND	33.3	5.7	3.1	ND	ND	31.8	9.1
Henkens et al. (36)	27	63.0	0	ND	ND	22	5.6	2.8	ND	ND	30.8	8.2
Gengsakul et al. (37)	82	50.0	0	2.4	ND	50	9	6.8	18.9	10	27.9	13.1
Oosterhof et al. (38)	71	59.2	0	1.4	4.2	33.8	5	2.7–7.4 IQR	ND	ND	29	23–37
Ghez et al. (39)	19	52.6	0	ND	ND	15.7	ND	ND	19.3	9.1	23.9	14
Oosterhof et al. (40)	158	59.5	0	2	9.5	38	6.3	1.5–11.2	ND	ND	29	13–45
Kleinveld et al. (41)	10	ND	0	ND	ND	70	2.1	0.7	ND	ND	11.5	2
Therrien et al. (42)	17	41.2	0	ND	ND	88.2	12.1	10.6	25	9	34	12
Buechel et al. (43)	20	ND	0	ND	ND	55	1.9	1.1	12	3	13.9	3
Doughan et al. (44)	21	28.6	0	ND	ND	44	ND	ND	28	5	34	9
van Huysduynen et al. (45)	26	57.7	0	ND	ND	38	5	2.8–6.8 IQR	ND	ND	29.2	24.3–39.4

Continued on the next page

Table 1 Continued

First Author (Ref. #)	Sample (N)	Sex, Male	30-Day Mortality	5-Yr Mortality	5-Yr Redo-PVR	Additional Procedures	Age at Fallot Repair Mean/Median (SD or Range)		Time Interval TOF Repair to PVR Mean/Median (SD or Range)		Age at PVR Mean/Median (SD or Range)	
van Straten et al. (46)	16	62.5	0	ND	ND	37.5	4.9	0.9–13.1	ND	ND	28.7	19.5–45.6
Borowski et al. (47)	18	66.7	5.6	ND	ND	16.6	5.1	3.9	18.5	7.8	23.6	11.1
Lim et al. (48)	58	65.5	2.5	2.5	12.1	72	5.2	7.1	8.3	5.2	13.5	9.6
Cesnjevar et al. (49)	47	ND	2.1	2.1	6.4	74	5.7	9.2	13.2	7.4	19.2	12.2
Warner et al. (50)	36	63.9	0	2.8	2.8	50	3.2	4.1	12.2	6.9	15.2	9.2
de Ruijter et al. (51)	16	ND	6.2	ND	ND	ND	1.9	2.5	9.2	ND	9.25	ND
Vliegen et al. (9)	26	57.7	0	ND	ND	15	5	4.2	ND	ND	29.2	9
Discigil et al. (52)	42	61.9	2	4.9	6.9	88	11.2	14.8	10.8	ND	22	16.4
Therrien et al. (53)	70	47.1	4	8	ND	48	7	1–40	16.8	ND	27.8	11.9
Eyskens et al. (54)	18	ND	ND	ND	ND	ND	3.5	3.1	10.1	4.1	13.5	5.7
Therrien et al. (55)	25	56.0	0	ND	ND	40	12.1	10.6	21.8	8.2	33.9	9.2
Yemets et al. (56)	85	63.5	1.1	1.1	2.3	66	5.6	0.5–40.0	9.3	0.4–36.0	19.6	ND

Values are percentages, unless otherwise indicated.
IQR = interquartile range; ND = not determined; PVR = pulmonary valve replacement; TOF = tetralogy of Fallot.

pooled 5-year re-PVR was 4.9% (15 studies; 88 of 1,798 patients).

The difference in means for indexed RVEDV after PVR in each study is reported in Figure 2A. Twenty-two studies reported the data. There was evidence for important heterogeneity of treatment effect among the studies for indexed RVEDV. The overall difference in means of indexed RVEDV showed a significant reduction after PVR (random-effects model: -62.734, SE $= 2.591$, $p < 0.001$).

The difference in means for indexed RVESV after PVR in each study is reported in Figure 2B. Eighteen studies reported the data. There was evidence for important heterogeneity of treatment effect among the studies for indexed RVESV. The overall difference in means of indexed RVESV showed a significant reduction after PVR (random-effects model: -38.091, SE $= 2.420$, $p < 0.001$).

The difference in means for PRF after PVR in each study is reported in Figure 2C. Fifteen studies reported the data. There was evidence for important heterogeneity of treatment effect among the studies for PRF. The overall difference in means of PRF showed significant reduction after PVR (random-effects model: -38.518, SE $= 0.920$, $p < 0.001$).

The difference in means for indexed LVEDV after PVR in each study is reported in Figure 3A. Fifteen studies reported the data. There was evidence for no heterogeneity of treatment effect among the studies for indexed LVEDV. The overall difference in means of indexed LVEDV showed a significant increase after PVR (random-effects model: 6.699, SE $= 0.683$, $p < 0.001$).

The difference in means for indexed LVESV after PVR in each study is reported in Figure 3B. Eleven studies reported the data. There was evidence for important heterogeneity of treatment effect among the studies for indexed LVESV. The overall difference in means of indexed LVESV showed no significant difference after PVR (random-effects model: 1.437, SE $= 0.990$, $p = 0.147$).

The difference in means for LVEF after PVR in each study is reported in Figure 3C. Seventeen studies reported the data. There was evidence for important heterogeneity of treatment effect among the studies for LVEF. The overall difference in means of LVEF showed significant increase after PVR (random-effects model: 1.821, SE $=$ 0.658, $p = 0.006$).

The difference in means for the RV/LV ratio (indexed RVEDV/indexed LVEDV) after PVR in each study is reported in Figure 4A. Six studies reported the data. There was evidence for important heterogeneity of treatment effect among the studies for RV/LV ratio. The overall difference in means of RV/LV ratio showed significant reduction after PVR (random-effects model: -0.922, SE $= 0.094$, $p < 0.001$).

The difference in means for QRS after PVR in each study is reported in Figure 4B. Twenty studies reported the data. There was evidence for nonsignificant heterogeneity of treatment effect for QRS among the studies. The overall difference in means of QRS showed a significant

Table 2 Analysis of Risk of Bias: Internal Validity

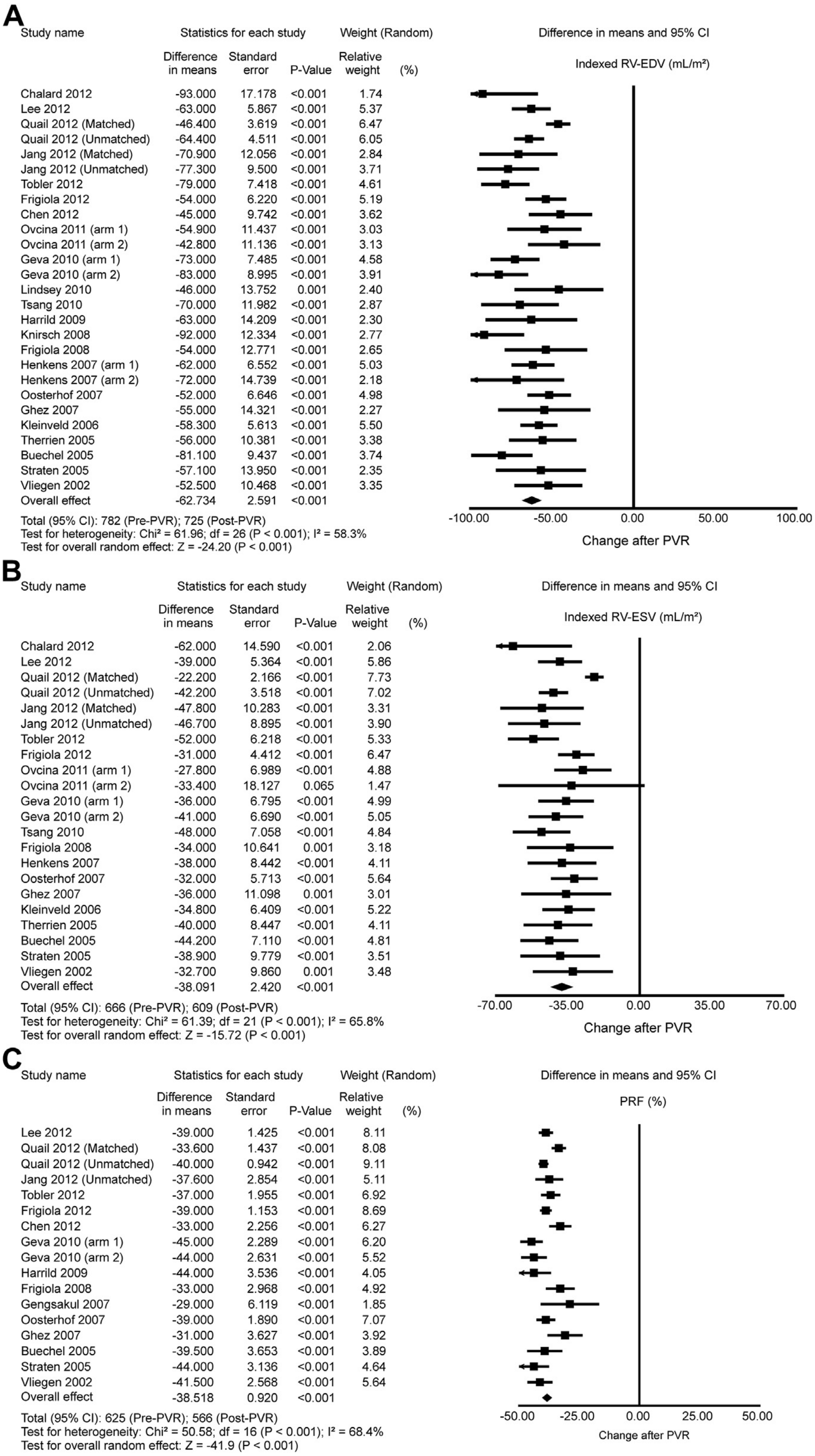
First Author (Ref. #)	Study Design	Selection Bias	Performance Bias	Detection Bias	Attrition Bias
Chalard et al. (10)	P, R, NM	B	A	A	A
Lee et al. (11)	NP, NR, NM	B	B	A	A
Quail et al. (12)	P, NR, NM	B	B	A	A
Jang et al. (13)	NP, NR, NM	B	B	C	C
Tobler et al. (14)	NP, NR, NM	B	B	A	A
Shiokawa et al. (15)	NP, NR, NM	B	B	C	A
Jain et al. (16)	NP, NR, NM	C	D	D	D
Batlivala et al. (17)	NP, NR, NM	C	D	D	D
Frigiola et al. (18)	P, NR, NM	C	B	B	A
Chen et al. (19)	NP, NR, NM	B	B	B	A
Chen et al. (20)	NP, NR, NM	B	B	B	A
Zubairi et al. (21)	NP, NR, NM	B	D	D	D
Ovcina et al. (22)	P, NR, NM	B	B	A	A
Kane et al. (23)	NP, NR, NM	C	B	B	A
Geva et al. (24)	P, R, NM	A	A	A	A
Shinkawa et al. (25)	NP, NR, NM	B	D	D	D
Scherptong et al. (26)	P, NR, M	B	A	A	A
Lindsey et al. (27)	NP, NR, NM	B	B	B	A
Tsang et al. (28)	NP, NR, NM	B	C	C	C
Harrild et al. (29)	NP, NR, NM	B	B	B	A
Dos et al. (30)	NP, NR, NM	B	D	D	D
Meijboom et al. (31)	NP, NR, NM	B	B	B	B
Graham et al. (32)	NP, NR, M	B	D	D	D
Knirsch et al. (33)	NP, NR, NM	B	B	A	A
Frigiola et al. (34)	P, NR, M	B	B	A	A
van Huysduynen et al. (35)	NP, NR, NM	B	B	A	A
Henkens et al. (36)	P, NR, NM	B	B	A	A
Gengsakul et al. (37)	NP, NR, NM	B	B	A	A
Oosterhof et al. (38)	P, NR, M	B	B	A	A
Ghez et al. (39)	NP, NR, M	B	C	C	A
Oosterhof et al. (40)	NP, NR, M	B	B	A	A
Kleinveld et al. (41)	NP, NR, M	B	B	A	A
Therrien et al. (42)	NP, NR, NM	B	B	A	A
Buechel et al. (43)	P, NR, M	B	B	A	A
Doughan et al. (44)	NP, NR, NM	B	B	A	A
van Huysduynen et al. (45)	NP, NR, NM	B	B	A	A
van Straten et al. (46)	NP, NR, NM	C	A	A	A
Borowski et al. (47)	NP, NR, NM	B	D	D	D
Lim et al. (48)	NP, NR, NM	B	D	D	D
Cesnjevar et al. (49)	NP, NR, NM	B	D	D	D
Warner et al. (50)	NP, NR, NM	B	D	D	D
de Ruijter et al. (51)	NP, NR, NM	B	D	D	D
Vliegen et al. (9)	NP, NR, NM	B	B	A	A
Discigil et al. (52)	NP, NR, NM	B	D	D	D
Therrien et al. (53)	NP, NR, M	B	A	A	A
Eyskens et al. (54)	NP, NR, NM	B	B	A	A
Therrien et al. (55)	NP, NR, NM	A	A	A	A
Yemets et al. (56)	NP, NR, NM	B	D	D	D

A = risk of bias is low; B = risk of bias is moderate; C = risk of bias is high; D = incomplete reporting; M = multicenter; NM = non-multicenter; NP = non-prospective; NR = non-randomized; P = prospective; R = randomized.

reduction after PVR (random-effects model: −2.861, SE = 1.385, p = 0.039).

The difference in means for NYHA after PVR in each study is reported in Figure 4C. Twenty-six studies reported the data. There was evidence for important heterogeneity of treatment effect among the studies for NYHA. The overall difference in means of NYHA showed a significant reduction after PVR (random-effects model: −0.855, SE = 0.097, $p < 0.001$).

Risk of bias across studies. Funnel plot analysis (Figs. 5 and 6) disclosed asymmetry around the axis for the treatment effect in the following outcomes: indexed RVESV; indexed



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Study name	Difference in means	Standard error	P-Value	Relative weight (%)
Chalard 2012	-93.000	17.178	<0.001	1.74
Lee 2012	-63.000	5.867	<0.001	5.37
Quail 2012 (Matched)	-46.400	3.619	<0.001	6.47
Quail 2012 (Unmatched)	-64.400	4.511	<0.001	6.05
Jang 2012 (Matched)	-70.900	12.056	<0.001	2.84
Jang 2012 (Unmatched)	-77.300	9.500	<0.001	3.71
Tobler 2012	-79.000	7.418	<0.001	4.61
Frigiola 2012	-54.000	6.220	<0.001	5.19
Chen 2012	-45.000	9.742	<0.001	3.62
Ovcina 2011 (arm 1)	-54.900	11.437	<0.001	3.03
Ovcina 2011 (arm 2)	-42.800	11.136	<0.001	3.13
Geva 2010 (arm 1)	-73.000	7.485	<0.001	4.58
Geva 2010 (arm 2)	-83.000	8.995	<0.001	3.91
Lindsey 2010	-46.000	13.752	0.001	2.40
Tsang 2010	-70.000	11.982	<0.001	2.87
Harrild 2009	-63.000	14.209	<0.001	2.30
Knirsch 2008	-92.000	12.334	<0.001	2.77
Frigiola 2008	-54.000	12.771	<0.001	2.65
Henkens 2007 (arm 1)	-62.000	6.552	<0.001	5.03
Henkens 2007 (arm 2)	-72.000	14.739	<0.001	2.18
Oosterhof 2007	-52.000	6.646	<0.001	4.98
Ghez 2007	-55.000	14.321	<0.001	2.27
Kleinveld 2006	-58.300	5.613	<0.001	5.50
Therrien 2005	-56.000	10.381	<0.001	3.38
Buechel 2005	-81.100	9.437	<0.001	3.74
Straten 2005	-57.100	13.950	<0.001	2.35
Vliegen 2002	-52.500	10.468	<0.001	3.35
Overall effect	-62.734	2.591	<0.001	

Weight (Random)

Total (95% CI): 782 (Pre-PVR); 725 (Post-PVR)
Test for heterogeneity: Chi² = 61.96; df = 26 (P < 0.001); I² = 58.3%
Test for overall random effect: Z = -24.20 (P < 0.001)

B

Study name	Difference in means	Standard error	P-Value	Relative weight (%)
Chalard 2012	-62.000	14.590	<0.001	2.06
Lee 2012	-39.000	5.364	<0.001	5.86
Quail 2012 (Matched)	-22.200	2.166	<0.001	7.73
Quail 2012 (Unmatched)	-42.200	3.518	<0.001	7.02
Jang 2012 (Matched)	-47.800	10.283	<0.001	3.31
Jang 2012 (Unmatched)	-46.700	8.895	<0.001	3.90
Tobler 2012	-52.000	6.218	<0.001	5.33
Frigiola 2012	-31.000	4.412	<0.001	6.47
Ovcina 2011 (arm 1)	-27.800	6.989	<0.001	4.88
Ovcina 2011 (arm 2)	-33.400	18.127	0.065	1.47
Geva 2010 (arm 1)	-36.000	6.795	<0.001	4.99
Geva 2010 (arm 2)	-41.000	6.690	<0.001	5.05
Tsang 2010	-48.000	7.058	<0.001	4.84
Frigiola 2008	-34.000	10.641	0.001	3.18
Henkens 2007	-38.000	8.442	<0.001	4.11
Oosterhof 2007	-32.000	5.713	<0.001	5.64
Ghez 2007	-36.000	11.098	0.001	3.01
Kleinveld 2006	-34.800	6.409	<0.001	5.22
Therrien 2005	-40.000	8.447	<0.001	4.11
Buechel 2005	-44.200	7.110	<0.001	4.81
Straten 2005	-38.900	9.779	<0.001	3.51
Vliegen 2002	-32.700	9.860	0.001	3.48
Overall effect	-38.091	2.420	<0.001	

Weight (Random)

Total (95% CI): 666 (Pre-PVR); 609 (Post-PVR)
Test for heterogeneity: Chi² = 61.39; df = 21 (P < 0.001); I² = 65.8%
Test for overall random effect: Z = -15.72 (P < 0.001)

C

Study name	Difference in means	Standard error	P-Value	Relative weight (%)
Lee 2012	-39.000	1.425	<0.001	8.11
Quail 2012 (Matched)	-33.600	1.437	<0.001	8.08
Quail 2012 (Unmatched)	-40.000	0.942	<0.001	9.11
Jang 2012 (Unmatched)	-37.600	2.854	<0.001	5.11
Tobler 2012	-37.000	1.955	<0.001	6.92
Frigiola 2012	-39.000	1.153	<0.001	8.69
Chen 2012	-33.000	2.256	<0.001	6.27
Geva 2010 (arm 1)	-45.000	2.289	<0.001	6.20
Geva 2010 (arm 2)	-44.000	2.631	<0.001	5.52
Harrild 2009	-44.000	3.536	<0.001	4.05
Frigiola 2008	-33.000	2.968	<0.001	4.92
Gengsakul 2007	-29.000	6.119	<0.001	1.85
Oosterhof 2007	-39.000	1.890	<0.001	7.07
Ghez 2007	-31.000	3.627	<0.001	3.92
Buechel 2005	-39.500	3.653	<0.001	3.89
Straten 2005	-44.000	3.136	<0.001	4.64
Vliegen 2002	-41.500	2.568	<0.001	5.64
Overall effect	-38.518	0.920	<0.001	

Weight (Random)

Total (95% CI): 625 (Pre-PVR); 566 (Post-PVR)
Test for heterogeneity: Chi² = 50.58; df = 16 (P < 0.001); I² = 68.4%
Test for overall random effect: Z = -41.9 (P < 0.001)

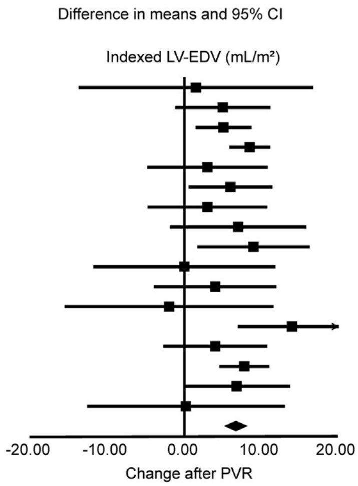
Figure 2 **Forest Plots of Clinical Outcomes of the Right Heart**

Pooled difference in means for **(A)** indexed right ventricular end-diastolic volume (RVEDV), **(B)** indexed right ventricular end-systolic volume (RVESV), and **(C)** pulmonary regurgitation fraction (PRF) after pulmonary valve replacement (PVR). CI = confidence interval.

A

Study name	Difference in means	Standard error	P-Value	Relative weight (%)
Chalard 2012	1.500	7.740	0.846	0.78
Lee 2012	5.000	3.115	0.108	4.81
Quail 2012 (Matched)	5.100	1.826	0.005	14.00
Quail 2012 (Unmatched)	8.500	1.318	<0.001	26.87
Tobler 2012	3.000	3.965	0.449	2.97
Frigiola 2012	6.000	2.742	0.029	6.21
Geva 2010 (arm 1)	3.000	3.941	0.446	3.01
Geva 2010 (arm 2)	7.000	4.479	0.118	2.33
Tsang 2010	9.000	3.691	0.015	3.43
Knirsch 2008	0.000	6.010	1.000	1.29
Frigiola 2008	4.000	4.024	0.320	2.88
Henkens 2007	-2.000	6.899	0.772	0.98
Oosterhof 2007	14.000	3.554	<0.001	3.70
Ghez 2007	4.000	3.411	0.241	4.01
Kleinveld 2006	7.800	1.617	<0.001	17.84
Buechel 2005	6.800	3.507	0.053	3.79
Vliegen 2002	0.200	6.525	0.976	1.10
Overall effect	6.699	0.683	<0.001	

Statistics for each study; Weight (Random)

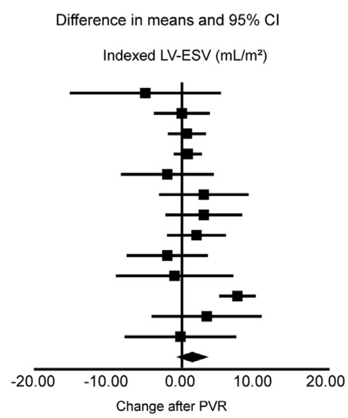


Total (95% CI): 540 (Pre-PVR); 536 (Post-PVR)
Test for heterogeneity: Chi² = 15.18; df = 16 (P = 0.512); I² = 0.0%
Test for overall random effect: Z = 9.80 (P < 0.001)

B

Study name	Difference in means	Standard error	P-Value	Relative weight (%)
Chalard 2012	-5.000	5.238	0.340	2.90
Lee 2012	0.000	1.908	1.000	9.77
Quail 2012 (Matched)	0.700	1.291	0.588	12.17
Quail 2012 (Unmatched)	0.800	0.943	0.396	13.47
Tobler 2012	-2.000	3.203	0.532	5.89
Geva 2010 (arm 1)	3.000	3.077	0.330	6.18
Geva 2010 (arm 2)	3.000	2.631	0.254	7.36
Tsang 2010	2.000	2.016	0.321	9.38
Frigiola 2008	-2.000	2.795	0.474	6.90
Henkens 2007	-1.000	4.060	0.805	4.28
Kleinveld 2006	7.600	1.232	<0.001	12.40
Buechel 2005	3.400	3.800	0.371	4.70
Vliegen 2002	-0.200	3.865	0.959	4.59
Overall effect	1.437	0.990	0.147	

Statistics for each study; Weight (Random)

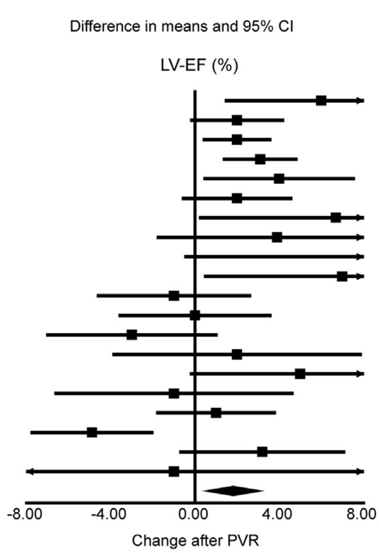


Total (95% CI): 362 (Pre-PVR); 358 (Post-PVR)
Test for heterogeneity: Chi² = 31.05; df = 12 (P = 0.002); I² = 61.3%
Test for overall random effect: Z = 1.45 (P = 0.147)

C

Study name	Difference in means	Standard error	P-Value	Relative weight (%)
Chalard 2012	6.000	2.325	0.010	4.49
Lee 2012	2.000	1.126	0.076	7.86
Quail 2012 (Matched)	2.000	0.816	0.014	8.83
Quail 2012 (Unmatched)	3.100	0.891	0.001	8.61
Tobler 2012	4.000	1.826	0.028	5.72
Frigiola 2012	2.000	1.324	0.131	7.23
Shiokawa 2012	6.700	3.309	0.043	2.85
Ovcina 2011 (arm 1)	3.900	2.902	0.179	3.42
Ovcina 2011 (arm 2)	8.600	4.633	0.063	1.68
Kane 2011	7.000	3.340	0.036	2.81
Geva 2010 (arm 1)	-1.000	1.855	0.590	5.64
Geva 2010 (arm 2)	0.000	1.839	1.000	5.68
Harrild 2009	-3.000	2.065	0.146	5.09
Knirsch 2008	2.000	3.010	0.506	3.25
Frigiola 2008	5.000	2.664	0.061	3.82
Henkens 2007	-1.000	2.887	0.729	3.44
Oosterhof 2007	1.000	1.439	0.487	6.86
Kleinveld 2006	-4.900	1.476	0.001	6.75
Buechel 2005	3.200	1.998	0.109	5.26
Doughan 2005	-1.000	7.545	0.895	0.71
Overall effect	1.821	0.658	0.006	

Statistics for each study; Weight (Random)



Total (95% CI): 595 (Pre-PVR); 591 (Post-PVR)
Test for heterogeneity: Chi² = 46.8; df = 19 (P < 0.001); I² = 59.4%
Test for overall random effect: Z = 2.77 (P = 0.006)

Figure 3 **Forest Plots of Clinical Outcomes of the Left Heart**

Pooled difference in means for **(A)** indexed LVEDV, **(B)** indexed LVESV, and **(C)** left ventricular ejection fraction (LVEF) after PVR. Abbreviations as in Figure 2.

A

Study name	Difference in means	Standard error	P-Value	Relative weight (%)
Lee 2012	-1.000	0.071	<0.001	19.14
Quail 2012	-0.700	0.027	<0.001	21.12
Tobler 2012	-1.100	0.115	<0.001	16.25
Frigiola 2008	-0.800	0.141	<0.001	14.48
Ghez 2007	-0.840	0.186	<0.001	11.72
Kleinveld 2006	-1.100	0.100	<0.001	17.30
Overall effect	-0.922	0.094	<0.001	

Statistics for each study; Weight (Random)

Total (95% CI): 185 (Pre-PVR); 185 (Post-PVR)
Test for heterogeneity: Chi² = 36.38; df = 5 (P < 0.001); I² = 86.3%
Test for overall random effect: Z = -9.79 (P < 0.001)

B

Study name	Difference in means	Standard error	P-Value	Relative weight (%)
Chalard 2012	-0.500	7.883	0.949	2.74
Lee 2012	-6.000	2.987	0.045	11.36
Jang 2012	1.200	3.663	0.743	8.97
Tobler 2012	-7.000	6.229	0.261	4.10
Shiokawa 2012	-19.600	8.659	0.024	2.31
Shinkawa 2010	-3.400	6.148	0.580	4.19
Scherptong 2010	-4.000	4.552	0.380	6.69
Tsang 2010	-4.000	11.102	0.719	1.46
Harrild 2009	-3.400	5.731	0.553	4.70
Meijboom 2008	-22.000	10.447	0.035	1.64
Knirsch 2008	-6.000	7.850	0.445	2.76
Huysduynen 2008	-5.000	8.524	0.558	2.38
Gengsakul 2007	4.000	3.392	0.238	9.86
Oosterhof 2007	-11.000	4.902	0.025	6.00
Kleinveld 2006	4.900	3.217	0.128	10.48
Buechel 2005	-2.000	5.836	0.732	4.57
Dougham 2005	-11.000	9.752	0.259	1.86
Huysduynen 2005	-7.000	8.183	0.392	2.56
Lim 2004	2.000	5.595	0.721	4.89
Therrien 2001	-2.000	4.654	0.667	6.48
Overall effect	-2.861	1.385	0.039	

Statistics for each study; Weight (Random)

Total (95% CI): 991 (Pre-PVR); 989 (Post-PVR)
Test for heterogeneity: Chi² = 24.50; df = 19 (P = 0.178); I² = 22.5%
Test for overall random effect: Z = -2.05 (P = 0.039)

C

Study name	Difference in means	Standard error	P-Value	Relative weight (%)
Chalard 2012	-0.600	0.176	0.001	3.72
Lee 2012	-0.600	0.051	<0.001	4.19
Tobler 2012	-0.600	0.101	<0.001	4.05
Shiokawa 2012	-1.200	0.205	<0.001	3.56
Ovcina 2011 (arm 1)	-1.900	0.073	<0.001	4.14
Ovcina 2011 (arm 2)	-1.300	0.242	<0.001	3.35
Geva 2010	-0.500	0.103	<0.001	4.05
Shinkawa 2010	-0.800	0.102	<0.001	4.05
Scherptong 2010	-1.100	0.097	<0.001	4.07
Knirsch 2008	-0.200	0.146	0.170	3.87
Frigiola 2008	-0.600	0.180	0.001	3.70
Henkens 2007	-0.700	0.129	<0.001	3.94
Gengsakul 2007	-0.600	0.093	<0.001	4.08
Oosterhof 2007	-0.900	0.139	<0.001	3.90
Ghez 2007	-0.800	0.196	<0.001	3.61
Therrien 2005	-0.600	0.271	0.027	3.18
Borowski 2004	-0.700	0.238	0.003	3.38
Lim 2004	-0.470	0.124	<0.001	3.97
Cesnjevar 2004	-1.470	0.094	<0.001	4.08
Warner 2003	-0.900	0.107	<0.001	4.03
Vliegen 2002	-0.700	0.153	<0.001	3.83
Ruijter 2002	-1.600	0.207	<0.001	3.56
Discigil 2001	-1.500	0.148	<0.001	3.86
Therrien 2001	-0.200	0.104	0.055	4.04
Therrien 2000	-0.500	0.180	0.005	3.70
Yemets 1997	-1.200	0.092	<0.001	4.08
Overall effect	-0.855	0.097	<0.001	

Statistics for each study; Weight (Random)

Total (95% CI): 1152 (Pre-PVR); 1140 (Post-PVR)
Test for heterogeneity: Chi² = 438.88; df = 25 (P < 0.001); I² = 94.3%
Test for overall random effect: Z = -8.82 (P < 0.001)

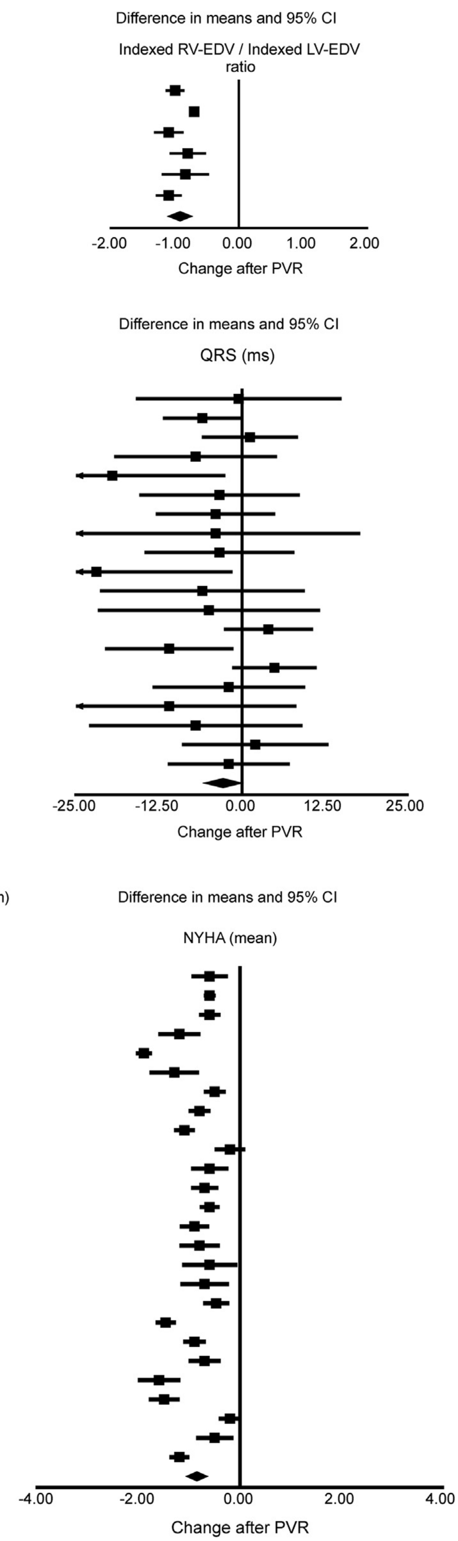


Figure 4 **Forest Plots of Clinical Outcomes**

Pooled difference in means for **(A)** RV/LV ratio, **(B)** QRS duration, and **(C)** New York Heart Association (NYHA) functional class after PVR. Abbreviations as in Figure 2.

LVEDV; and QRS. Consequently, we probably have publication bias related to these outcomes. Publication biases were not found in the other outcomes.

Sensitivity analysis. The difference in means for non-corrected RVEF after PVR in each study is reported in Figure 7A. Eighteen studies reported the data. There was evidence for important heterogeneity of treatment effect among the studies for non-corrected RVEF. The overall difference in means of non-corrected RVEF showed no significant difference after PVR (random-effects model: 1.004, SE = 0.856, p = 0.241).

The difference in means for corrected RVEF after PVR in each study is reported in Figure 7B. Only 4 studies reported the data with regard to this outcome. There was evidence for important heterogeneity of treatment effect among the studies for corrected RVEF. The overall difference in means of corrected RVEF showed significant increase after PVR (random-effects model: 21.275, SE = 2.913, p < 0.001).

Meta-regression analysis. With regard to pre-operative indexed RVEDV, we observed statistically significant coefficients for changes in post-operative indexed RVEDV (Fig. 8A), post-operative indexed RVESV (Fig. 8B), and

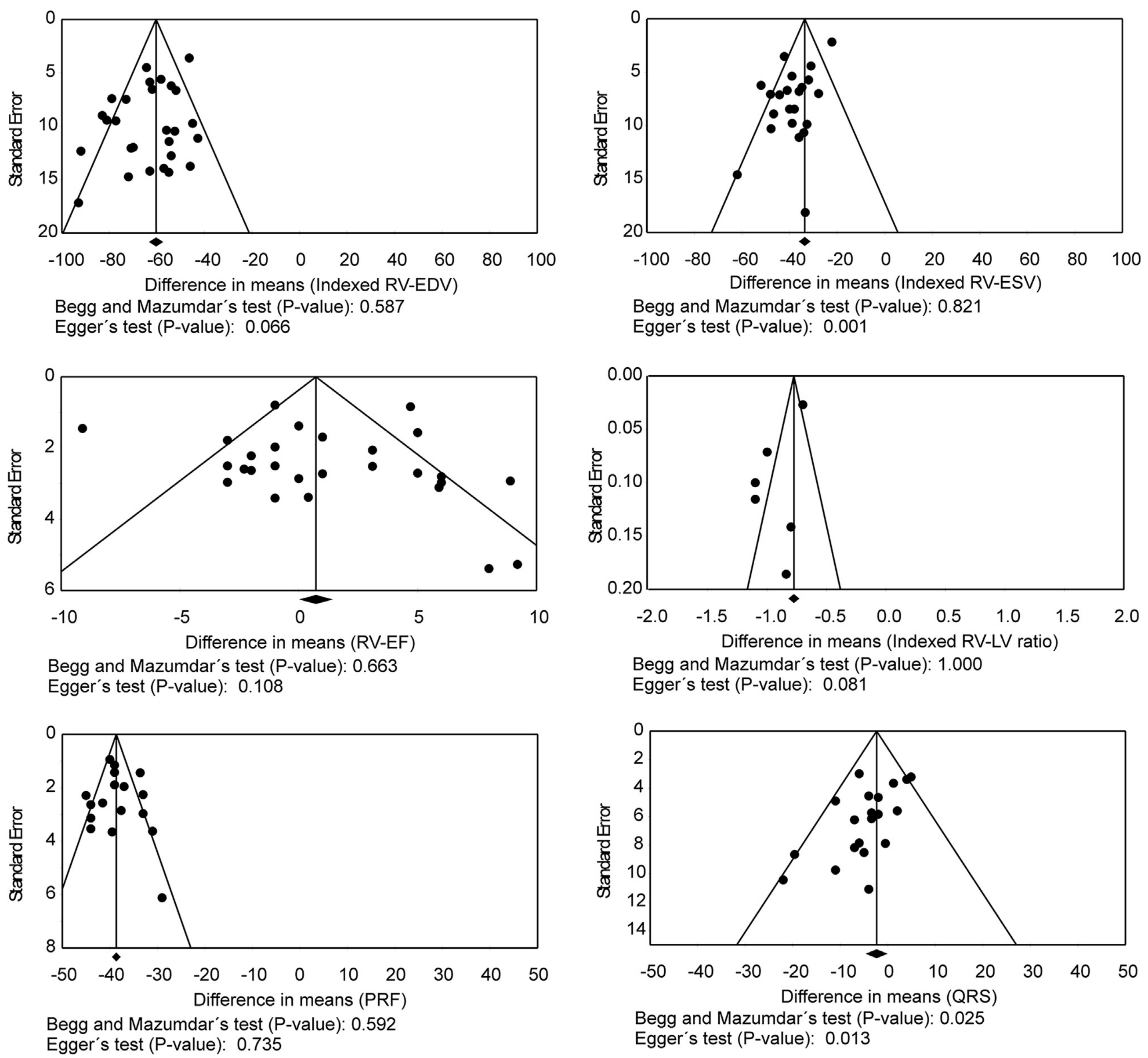


Figure 5 **Publication Bias Analysis of Clinical Outcomes by Funnel Plot Graphic**

Indexed RVEDV, indexed RVESV, right ventricular ejection fraction (RVEF), indexed RV/LV ratio, PRF, and QRS. Funnel plot analysis disclosed asymmetry around the axis for the treatment effect in indexed RVESV and QRS (p < 0.05 by Begg and Mazumdar's test or Egger's test). Abbreviations as in Figure 2.

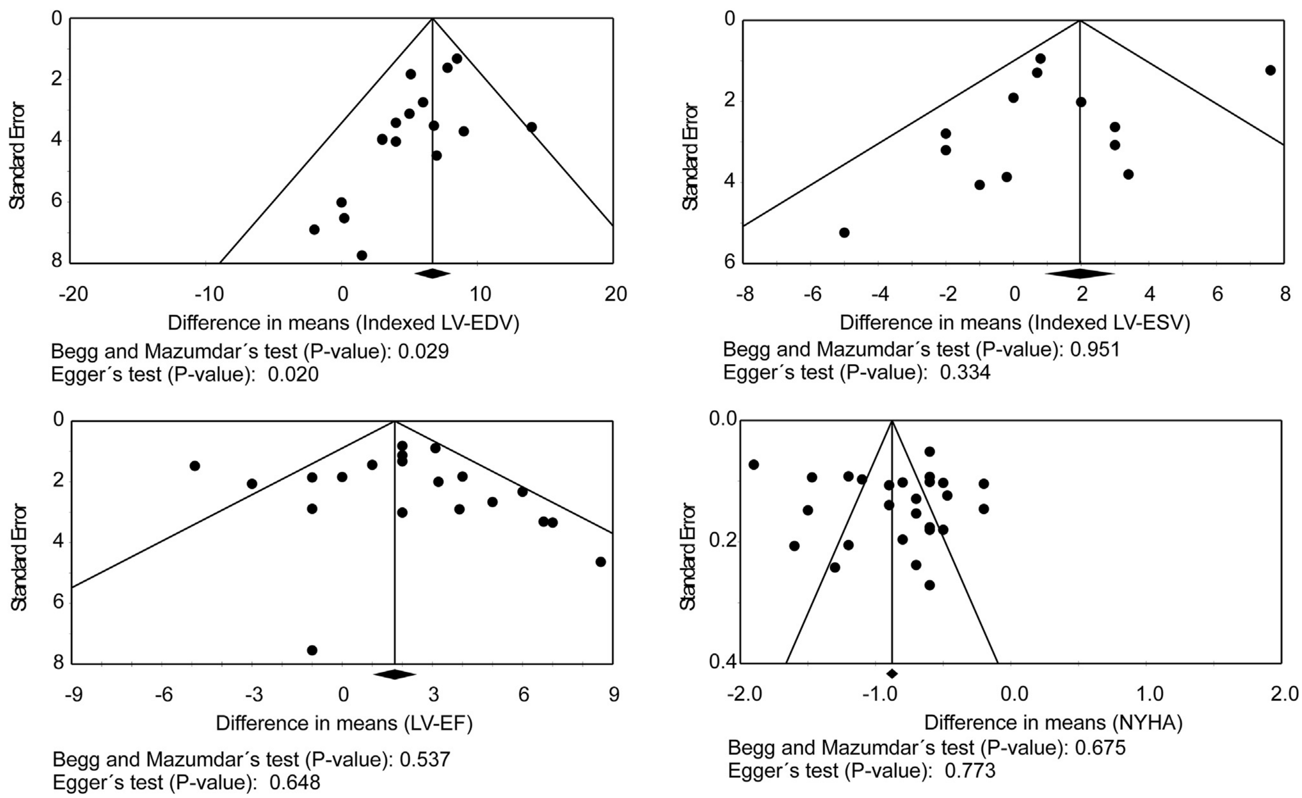


Figure 6 **Publication Bias Analysis of Clinical Outcomes by Funnel Plot Graphic**

Indexed LVEDV, indexed LVESV, LVEF, and NYHA functional class. Funnel plot analysis disclosed asymmetry around the axis for the treatment effect in indexed LVEDV ($p < 0.05$ by Begg and Mazumdar's test or Egger's test). Abbreviations as in Figure 4.

NYHA functional class (Fig. 8C). We can observe that the greater the pre-operative indexed RVEDV in a population undergoing PVR after TOF repair, the greater the decrease in post-operative indexed RVEDV and the greater the decrease in post-operative indexed RVESV but the lower the improvement in post-operative NYHA functional class.

Additionally, we observed statistically significant coefficients for proportion of additional surgical procedures concomitant to PVR and changes in post-operative indexed RVEDV (Fig. 8D). We can observe that the greater the proportion of additional surgical procedures in a population undergoing PVR after TOF repair, the greater the decrease in post-operative indexed RVEDV.

Concerning pre-operative indexed RVESV, we observed statistically significant coefficients for changes in post-operative indexed RVEDV (Fig. 9A) and post-operative indexed RVESV (Fig. 9B). We can observe that the greater the pre-operative indexed RVESV in a population undergoing PVR after TOF repair, the greater the decrease in post-operative indexed RVEDV and the greater the decrease in post-operative indexed RVESV.

With respect to PRF decrease, we observed statistically significant coefficients for changes in post-operative indexed RVEDV (Fig. 9C) and post-operative indexed RVESV (Fig. 9D). We can observe that the lower the PRF decrease in a population undergoing PVR after TOF repair, the lower the decrease in post-operative indexed RVEDV and the lower the decrease in post-operative indexed RVESV. In other words, we could say that the greater the PRF decrease, the greater the decrease in post-operative indexed RVEDV and the greater the decrease in post-operative indexed RVESV.

With regard to age at TOF repair, age at PVR, time from TOF repair to PVR, and sex, we observed no statistically significant coefficients, which means that these covariates did not modulate the effect of PVR on outcomes.

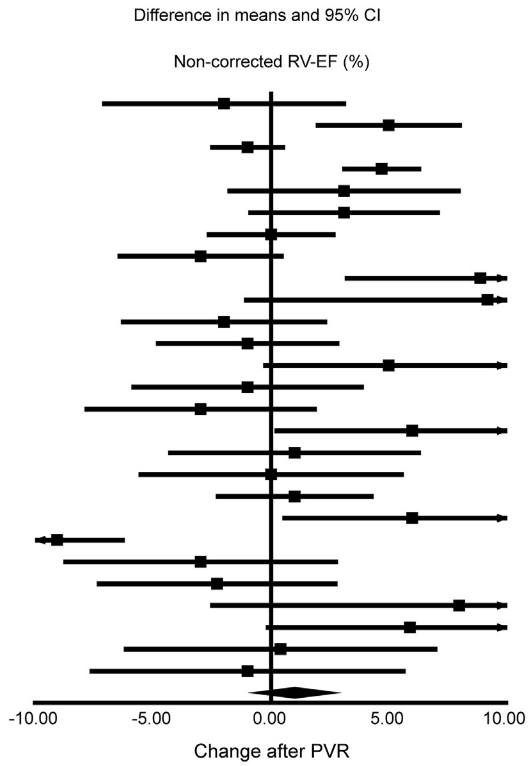
Discussion

Summary of evidence. To our knowledge, this is the largest meta-analysis of studies performed to date that provides incremental value by demonstrating that patients with repaired TOF who developed pulmonary insufficiency over time after PVR: 1) have a doubtless decrease in PRF; 2) present RV improvement of its indexed volumes but no improvement in ejection fraction (EF) (taking into account non-corrected measures); 3) present LV improvement of its systolic function measured by EF, despite the increasing of

A

Study name	Difference in means	Standard error	P-Value	Relative weight (%)
Chalard 2012	-2.000	2.628	0.447	3.58
Lee 2012	5.000	1.565	0.001	4.58
Quail 2012 (Matched)	-1.000	0.792	0.207	5.17
Quail 2012 (Unmatched)	4.700	0.838	<0.001	5.14
Jang 2012 (Matched)	3.100	2.513	0.217	3.69
Jang 2012 (Unmatched)	3.100	2.057	0.132	4.12
Tobler 2012	0.000	1.377	1.000	4.75
Chen 2012	-3.000	1.782	0.092	4.38
Ovcina 2011 (arm 1)	8.900	2.925	0.002	3.32
Ovcina 2011 (arm 2)	9.200	5.267	0.081	1.78
Geva 2010 (arm 1)	-2.000	2.217	0.367	3.97
Geva 2010 (arm 2)	-1.000	1.970	0.612	4.21
Tsang 2010	5.000	2.704	0.064	3.51
Harrild 2009	-1.000	2.500	0.689	3.70
Knirsch 2008	-3.000	2.500	0.230	3.70
Frigiola 2008	6.000	2.968	0.043	3.28
Henkens 2007	1.000	2.722	0.713	3.50
Gengsakul 2007	0.000	2.857	1.000	3.38
Oosterhof 2007	1.000	1.690	0.554	4.47
Ghez 2007	6.000	2.800	0.032	3.43
Kleinveld 2006	-9.100	1.448	<0.001	4.69
Therrien 2005	-3.000	2.961	0.311	3.29
Buechel 2005	-2.300	2.591	0.375	3.62
Doughan 2005	8.000	5.385	0.137	1.72
Straten 2005	5.900	3.105	0.057	3.16
Vliegen 2002	0.400	3.382	0.906	2.93
Therrien 2000	-1.000	3.406	0.769	2.92
Overall effect	1.004	0.856	0.241	

Statistics for each study; Weight (Random)

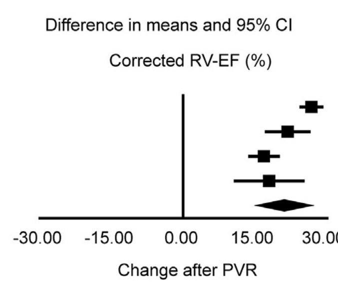


Total (95% CI): 752 (Pre-PVR); 704 (Post-PVR)
Test for heterogeneity: Chi² = 121.19; df = 26 (P < 0.001); I² = 78.5%
Test for overall random effect: Z = 1.17 (P = 0.241)

B

Study name	Difference in means	Standard error	P-Value	Relative weight (%)
Lee 2012	27.000	1.226	<0.001	28.20
Henkens 2007	22.000	2.394	<0.001	24.72
Oosterhof 2007	17.000	1.633	<0.001	27.15
Vliegen 2002	18.100	3.739	<0.001	19.93
Overall effect	21.275	2.913	<0.001	

Statistics for each study; Weight (Random)



Total (95% CI): 231 (Pre-PVR); 181 (Post-PVR)
Test for heterogeneity: Chi² = 26.03; df = 3 (P < 0.001); I² = 88.5%
Test for overall random effect: Z = 7.30 (P < 0.001)

Figure 7 **Forest Plots of the Sensitivity Analysis for Noncorrected and Corrected Measures of RVEF**

(A) Non-corrected RVEF. **(B)** Corrected RVEF. Abbreviations as in Figure 5.

its indexed diastolic volume and no change of its indexed systolic volume; 4) have a decrease of QRS duration; and 5) have an improvement of symptoms. Furthermore, if we consider the corrected RVEF measure, we observe that: 6) in fact, the RV experienced a real improvement of its systolic function; 7) RVs with greater pre-operative indexed RVEDV measures presented the best responses in terms of RV geometry in the post-operative period but were correlated to less improvement of symptoms, despite the improvement in RV geometry; 8) RVs with greater pre-operative indexed RVESV measures presented the best responses in terms of RV geometry in the post-operative period; 9) hearts with greater PRF decrease measures presented the best responses in terms of RV geometry in the post-operative period; 10) populations with greater proportions of additional procedures presented the best responses in terms of RV geometry in the post-operative period; 11) almost all these observations are under important influence of heterogeneity of the effects; and 12) we found virtually no publication bias.

Mortality. Our crude results with regard to pooled 30-day and 5-year mortality show that the rates seem to be acceptable, because they are both low. The low reporting of data about 10-year mortality limits any long-term analysis. Taking into consideration that almost all the studies reported data with regard to symptomatic patients, these results must not be used to stimulate aggressive management in asymptomatic patients.

Effect of PVR on RV. Since the first report by Vliegen et al. (9) about the improvement of RV parameters assessed by

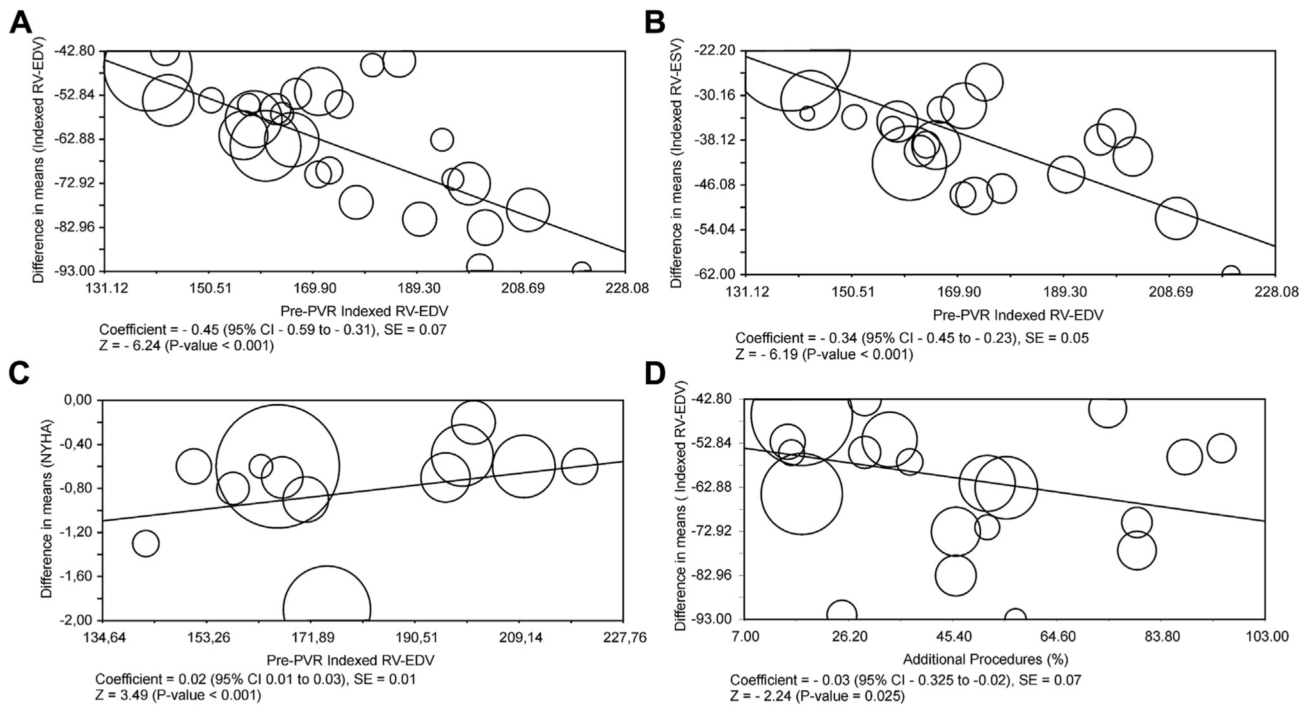


Figure 8 **Meta-Regression Analysis**

Correlation between a given factor (plotted as a mean or proportion of that factor on the x-axis) and the effect of PVR on the outcome (plotted on the y-axis). Each **circle** in the plot represents a study, and the circumference of each circle is proportional to study population size. **(A)** Pre-PVR–indexed RVEDV and difference in means (indexed RVEDV). **(B)** Pre-PVR–indexed RVEDV and difference in means (indexed RVESV). **(C)** Pre-PVR–indexed RVEDV and difference in means (NYHA). **(D)** Additional procedures and difference in means (indexed RVEDV). Abbreviations as in Figure 4.

cardiac MRI, several studies also observed these findings with the volumetric measures before and after PVR to better understand the response of the RV after removal of volume overload (10–14,18,19,22,24,27–29,33,34,36,38,39,41–43,46).

Having observed that some ventricles changed more than others and not all of them reached normal values, Therrien et al. (42) studied pre-operative parameters to evaluate the response to PVR and tried to find a threshold of volumetric measures above which there would be no more normalization of the ventricle. Only 17 patients were studied and, taking into account that no patients reached the normalization if the pre-operative indexed RVEDV was >170 ml/m^2 and RVESV was >85 ml/m^2, the author suggested that PVR should be undertaken before the reported values.

Having concluded that RV volumes decreased on average 28%, Oosterhof et al. (38) tried to find a cutoff value for normalization (57) of the RV volumes in an attempt to determine the optimal timing for the procedure and concluded that normalization could be achieved when pre-operative indexed RVEDV was <160 ml/m^2 or RVESV was <82 ml/m^2. It is very important to highlight that they were not able to find a threshold above which RV volumes did not decrease after surgery.

Geva et al. (24) studied a group of 64 patients in a randomized trial to investigate whether the addition of surgical RV remodeling to PVR would result in improved RV function when compared with PVR alone. They analyzed pre-operative factors associated with optimal (indexed RVEDV $\leq$114 ml/m^2 and RVEF $\geq$48%) and suboptimal (indexed RVEDV $\geq$120 ml/m^2 and RVEF $\leq$45%) outcomes (RV size and function were taken into account to determine an optimal post-operative outcome). Pre-operative indexed RVESV <90 ml/m^2 was associated with normalization of post-operative RV size and function, whereas pre-operative RVEF <45% was associated with persistent post-operative RV dilation and dysfunction.

Recently, Quail et al. (12) studied a cohort of 87 patients and compared intervention versus nonintervention, trying to establish whether delaying PVR would lead to short-term progressive deterioration in RV or LV dimensions or function, and it was observed that total normalization (57) of RVEDV and RVESV occurred in 64.7% of patients. It is noteworthy that no absolute upper threshold for normalization could be determined. Although the tendency for complete normalization decreased with increasing preoperative volumes, ventricles portraying very high preoperative RVEDV and RVESV measures reached normal values after PVR.

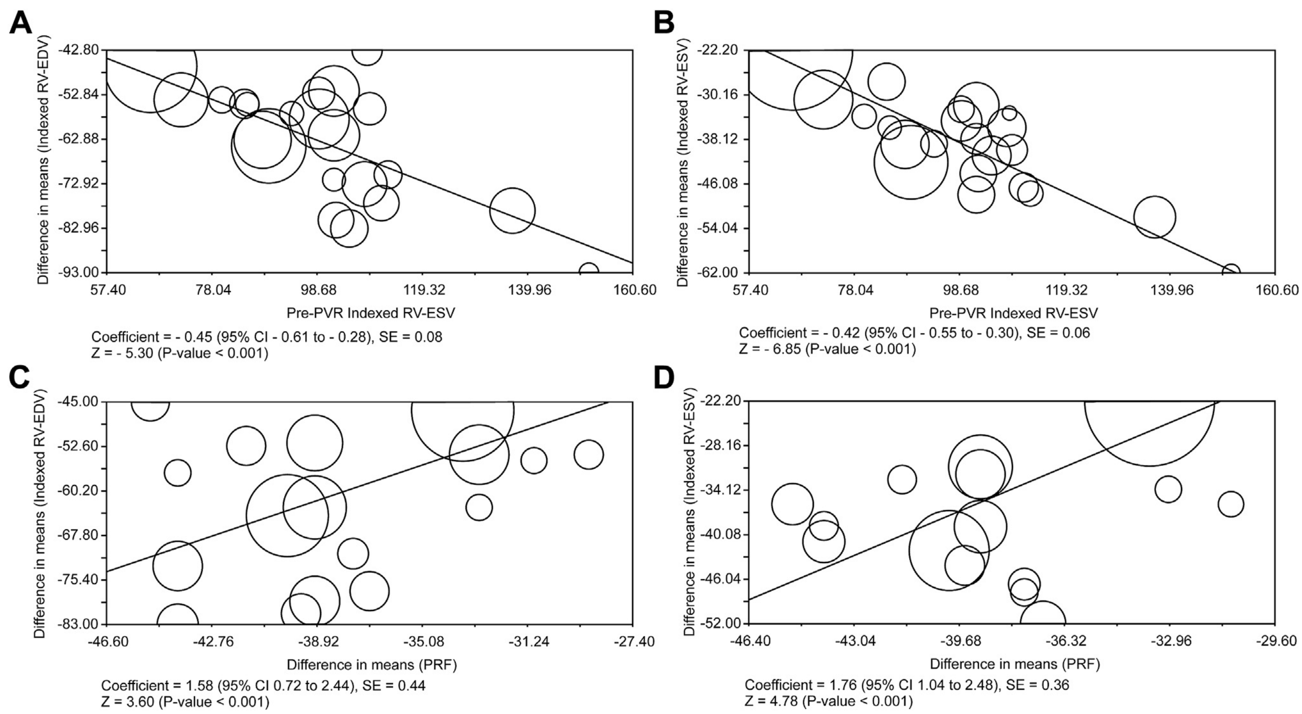


Figure 9 **Meta-Regression Analysis**

Correlation between a given factor (plotted as a mean or proportion of that factor on the x-axis) and the effect of PVR on the outcome (plotted on the y-axis). **(A)** Pre-PVR–indexed RVESV and difference in means (indexed RVEDV). **(B)** Pre-PVR–indexed RVESV and difference in means (indexed RVESV) **(C)** Difference in means (PRF) and difference in means (indexed RVEDV). **(D)** Difference in means (PRF) and difference in means (indexed RVESV). Abbreviations as in Figure 4.

We can observe that the evaluation of the RV response to the PVR seems to be under change, once normalization of the volumetric measures after procedure is not necessarily the target. The so-called upper threshold is difficult to establish, because recent findings tend to question the normal values as mentioned by Sarikouch et al. (58) and the relevance of sex.

The findings are in accordance with our study. After evaluating 22 studies (9–14,18,19,22,24,27–29,33,34,36, 38,39,41–43,46) that reported data about pre-operative and pos-toperative indexed RVEDV and 18 studies (9–14, 18,22,24,28,34,36,38,39,41–43,46) that reported indexed RVESV, we used the meta-regression and concluded that populations with greater pre-operative indexed RVEDV measures presented the best responses in terms of RV geometry change in the post-operative period. Likewise, populations with greater pre-operative indexed RVESV measures presented the best responses in terms of RV geometry change in the post-operative period. Paradoxically, populations with the greater pre-operative volumes presented lesser improvement of symptoms, despite the improvement in RV geometry.

Although the RVEF measures have been the most reported data among the studies included in this meta-analysis, these data were not able to demonstrate any difference after PVR in pooled results. This happened due the use of non-corrected measure for the presence of tricuspid and pulmonary regurgitation and residual shunts. However, when the reported studies used, not only the uncorrected measure, but the corrected one for these covariates, the difference emerged and revealed the RVEF improvement. Therefore, the non-corrected measure is not a reliable tool to assess RVEF before PVR.

Effect of PVR on LV and RV/LV interactions. A recent publication by Broberg et al. (59), after analysis of 511 patients with repaired TOF, concluded that the left systolic dysfunction assessed by conventional echocardiography was present in 21% of patients. When it comes to patients with previous PVR, the prevalence of LV systolic dysfunction increased to 52.4%, justifying the current tendency of studies to focus on LV.

Attention to the left side of the heart after Fallot repair was first given by Kondo et al. (60), who documented latent LV dysfunction during exercise. Davlouros et al. (61) assessed 85 adults with cardiac MRI and showed that LV systolic dysfunction correlated to RV dysfunction, suggesting an unfavorable ventricular × ventricular interaction. This finding was also demonstrated by Geva et al. (62).

Left ventricle response after pulmonary insufficiency correction, once RV volume overload is resolved, was documented by Frigiola et al. (34) studying 25 patients. They observed an increase in LVEDV after PVR, suggesting a better

LV filling due to an improved pulmonary forward flow and a left-to-right shift of interventricular septum. Another study from the same author (63) with 60 patients showed a significant reduction in RV volumes and increased LVEDV with a significant improvement in LV systolic function indexes (EF, effective stroke volume, and effective cardiac output).

The exact mechanism by which there is an improvement of LV systolic function after PVR might have a physiological explanation, as pointed out by Geva (64), when the author refers to the finding by French physiologist Bernheim in 1910, known as Bernheim's effect: the recognition of interdependence between LV and RV function, where alterations in the size and function of the LV have an adverse impact on the geometry and function of the RV (65). After PVR, resembling "reversed Bernheim effect" (66), the relief of RV volume overload leads to decreased septal shift toward the LV and augmentation in LV volumes. Furthermore, there are other mechanisms possibly involved in ventricular $\times$ ventricular interaction: the shared myofibers, septum, pericardium, and coronary flow.

Therefore, the increase of LV volumes after PVR must not be misinterpreted as worsening of its performance. Contrarily, it might signal an improvement. In the scenario where the enlargement of the RV/LV ratio represents RV deterioration and a trigger to PVR both for symptomatic and asymptomatic patients, the decrease of RV volumes and maybe the increase of LV volumes are goals to be achieved.

Effect of PVR on QRS duration. Tobler et al. (14) previously documented that QRS enlargement combined with LVEF reduction had the highest positive and negative predictive value for sudden cardiac death. Scherptong et al. (26) have suggested that sudden cardiac death after PVR relates to the magnitude of change in QRS duration postoperatively. Our meta-analysis identified reduction of QRS duration and LVEF improvement after PVR, which in combination might mean reduction of long-term mortality. Obviously, the latter statement is a mere speculation, and specific studies are required to confirm it.

Effect of PVR on symptoms. It is essential to reach the improvement of symptoms when the patients are confronted with a surgical option, because the presence of symptoms is stated as criteria for PVR by the current guidelines (1,2) and is the key point to assessing life quality. Our meta-analysis showed a clear decrease of symptoms after PVR. However, the meta-regression method demonstrated that studies with the greatest means of pre-operative indexed RVEDV had the greatest decrease in post-operative RV volumes but the lowest improvement in post-operative NYHA functional class.

These findings could lead us to think that we should not wait until the heart dilates too much, taking into consideration that it could minimize the benefits on symptoms after PVR.

Role of additional procedures. Additional/concomitant procedures to PVR were reported in 39 studies and ranged from 7.1% to 95%. It was not feasible to measure the real influence of these procedures through our meta-analysis. Maybe some observed benefits were modulated by these procedures. This last statement is supported by 1 of our meta-regressions, which demonstrated a clear correlation between rate of additional procedures and change in indexed RVEDV. This fact points to their role in the elimination of all structural abnormalities (inherent to TOF repair, residual or recurrent lesions, and acquired lesions).

The prevalence of structural and functional abnormalities after primary repair of Fallot is not negligible, as reported by the INDICATOR (International Multicenter TOF Registry) (67) cohort. This, in addition to the modulation of the effect by the prevalence of additional procedures, makes it unclear whether the benefits observed through PVR are mostly due to the elimination of pulmonary regurgitation or due to the resolution of multiple cardiac abnormalities existing at the time of PVR.

Risk of bias and limitations. This meta-analysis included data from nonrandomized and/or observational studies, which reflects the "real world," but they are limited by treatment bias, confounders, and a tendency to overestimate treatment effects. Patient selection alters outcome and thus makes nonrandomized studies obviously less robust.

It is difficult to compare and group these studies, because of many factors: patients might have been referred for surgery at different ages and times after primary repair, with different indications to PVR; different centers have different surgical routines; so many patients have additional lesions leading to a high percentage of additional procedures at time of PVR; there is a wide range of valves or valved conduits; and there is variability of follow-up length and many techniques used to assess RV function and volume after PVR.

There are inherent limitations with meta-analyses, including the use of cumulative data from summary estimates. Patient data were gathered from published data, not from individual patient follow-up. Access to individual patient data would have enabled us to conduct further subgroup analysis and propensity analysis to account for differences between the treatment groups.

Conclusions

Surgical PVR in patients after TOF repair has been associated with low 30-day and 5-year mortality rates; acceptable 5-year re-PVR rate; significant decreases in RV volumes and increase in RV systolic function; increase in both LV systolic function and volume; decrease in QRS duration; and improvement in functional class.

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